Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: A prospective, randomized, non-inferiority pilot trial

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Abstract: BACKGROUND In patients with diabetic foot osteomyelitis (DFO) who underwent surgical debridement, we investigated whether a short (3 weeks), compared with a long (6 weeks) duration of systemic antibiotic treatment is associated with non-inferior results for clinical remission and adverse events (AE). METHODS In this prospective, randomized, non-inferiority, pilot trial, we randomized (allocation 1:1), patients with DFO after surgical debridement to either a 3-week or a 6-week course of antibiotic therapy. The minimal duration of follow-up after end of therapy was two months. We compared outcomes using Cox regression and non-inferiority analyses (25% margin, power 80%). RESULTS Among 93 enrolled patients (18% females; median age 65 years), 44 were randomized to the 3-week arm and 49 to the 6-week arm. The median number of surgical debridement was 1 (range, 0-2 interventions). In the intention-to-treat (ITT) population, remission occurred in 37 (84%) of the patients in the 3-week arm compared to 36 (73%) in the 6-week arm (p=0.21). The number of AE was similar in the two study arms (17/44 vs. 16/49; p=0.51), as were the remission incidences in the per-protocol (PP) population (33/39 vs. 32/43; p=0.26). In multivariate analysis, treatment with the shorter antibiotic course was not significantly associated with remission (for the ITT population, hazard ratio 1.1, 95%CI 0.6-1.7; for the PP population hazard ratio 0.8, 95%CI 0.5-1.4). CONCLUSIONS In this randomized, controlled pilot trial, a post-debridement systemic antibiotic therapy course for DFO of 3-weeks gave similar (and statistically non-inferior) incidences of remission and AE to a course of 6 weeks.

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Three versus six weeks of antibiotic therapy for diabetic foot osteomyelitis: A prospective, randomized, non-inferiority pilot trial

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Summary:

In this prospective-randomized pilot trial investigating the duration of post-debridement antibiotic therapy for diabetic foot osteomyelitis, a short duration three weeks) was non-inferior to long duration (six weeks) for the outcomes of achieving clinical remission or the occurrence of antibiotic-related adverse events.

Summary

Background. In patients with diabetic foot osteomyelitis (DFO) who underwent surgical debridement, we investigated whether a short (3 weeks), compared with a long (6 weeks) duration of systemic antibiotic treatment is associated with non-inferior results for clinical remission and adverse events (AE).

Methods. In this prospective, randomized, non-inferiority, pilot trial, we randomized (allocation 1:1), patients with DFO after surgical debridement to either a 3-week or a 6-week course of antibiotic therapy. The minimal duration of follow-up after end of therapy was two months. We compared outcomes using Cox regression and non-inferiority analyses (25% margin, power 80%).

Results. Among 93 enrolled patients (18% females; median age 65 years), 44 were randomized to the 3-week arm and 49 to the 6-week arm. The median number of surgical debridement was 1 (range, 0-2 interventions). In the intention-to-treat (ITT) population, remission occurred in 37 (84%) of the patients in the 3-week arm compared to 36 (73%) in the 6-week arm (p=0.21). The number of AE was similar in the two study arms (17/44 vs. 16/49; p=0.51), as were the remission incidences in the per-protocol (PP) population (33/39 vs. 32/43; p=0.26). In multivariate analysis, treatment with the shorter antibiotic course was not significantly associated with remission (for the ITT population, hazard ratio 1.1, 95%CI 0.6-1.7; for the PP population hazard ratio 0.8, 95%CI 0.5-1.4).

Conclusions. In this randomized, controlled pilot trial, a post-debridement systemic antibiotic therapy course for DFO of 3-weeks gave similar (and statistically non-inferior) incidences of remission and AE to a course of 6 weeks.

Registration. Switzerland: BASEC 2016-01008; International: NCT03615807.

Keywords**:** diabetic foot osteomyelitis; antibiotic duration; infection remission; adverse events; randomized-controlled pilot trial

Introduction

Diabetic foot osteomyelitis (DFO) is associated with high financial costs, frequent recurrences, and lower extremity amputations [1-5]. Because of the high potential for poor outcomes, many clinicians treat DFOs with a long course (>6 weeks) of antibiotic therapy, despite the recommendation of guidelines to limit it to 4-6 weeks [1,3]. For example, a recent British analysis reported a duration of antibiotic therapy for DFO of less than six weeks in only 23% of cases, but of 3-6 months in 34% and >6 months in 7% [6]. Similarly, a Canadian paper reported a median duration of oral antimicrobial therapy for DFO of 40 ± 30 weeks [7]. There are, in fact, few published data supporting a prolonged therapy for DFO, yet such an approach certainly increases the risk of side effects, development of antibiotic resistance, and costs [8,9].

To help define proper antibiotic stewardship in DFO [2], we need randomized-controlled trials (RCT) comparing the key outcomes with different durations of therapy. However, RCTs in the diabetic foot are difficult. Confounding issues include the presence and treatment of peripheral arterial disease, poor glycemic control, degree of bone destruction, and overall adherence [1,2,8-12]. A pilot study is often appropriate to provide information to help determine the feasibility and proper design of a larger confirmatory RCT. Based on our experience in patients with diabetic foot infections (DFI) performing RCTs [13,14], and investigating antibiotic optimization, we designed this pilot RCT comparing short versus long duration of systemic antibiotic therapy for DFO.

Methods

Setting and timeline

We prospectively compared key outcomes of patients treated with a relatively short (3 weeks) versus a long (6 weeks) duration of antibiotic therapy for diabetic foot infection (DFI). The main (overall) trial had two stratifications: 1) soft tissue DFIs; and, 2) DFOs. For conciseness, we will publish the results for patients with soft tissue infections separately from this report. We began enrollment on 16 February 2017, enrolled the last participant on 1st October 2019, and closed the database on 31 March 2020. The Geneva Ethical Committee approved the RCT (BASEC 2016-01008), which we registered internationally (ClinicalTrials.gov NCT03615807).

Study Objectives and Criteria

We assessed the clinical remission of DFO at two months after the designated End of Treatment (EOT). By unblinded randomization, we allocated all participants, in a ratio of 1:1, to either a short antibiotic therapy arm of (3 weeks ± 2 days), or a long arm (6 weeks ± 2 days). The principal investigator (IU, or his replacements KG and TP) generated the allocation sequence in pre-fabricated sealed envelopes.

Inclusion criteria were: age ≥18 years; diagnosis of diabetes mellitus (by American Diabetes Association criteria); having undergone appropriate debridement of all necrotic tissue; and, the presence of DFO.

Exclusion criteria were: DFO associated with an implant; having received effective antibiotic therapy within the 96 previous hours; total clinical amputation of all infected tissue; complete destruction of bone beyond the cortical level; or,

remote infection of any type requiring more than 21 days of another antibiotic therapy; e.g. concomitant endocarditis or prosthetic joint infection (Study protocol; Appendix 1).

Treating clinicians were allowed to perform any needed wound debridement procedures, to choose the method of weight off-loading the affected foot, the appropriate diagnostic imaging methods [15], decide on the need for angioplasty, and to use negative-pressure vacuum therapy or hyperbaric oxygen for wound healing. While full resection of all infected bone was an exclusion, we permitted partial surgical amputation for necrotic bone. Our definition for "partial amputation" was purposely loose, including an amputation in one toe but leaving the DFO of another toe for conservative therapy, or a planned limited resection, such as during a partial calcanectomy [16,17]. If there was a partial amputation, we determined the presence of residual DFO by previous radiological and/or intraoperative assessments, and the decision to leave treat remaining DFO with antibiotic therapy. To limit the number of antibiotic drugs investigators might select, we provided a list of permitted agents from which the clinician could select the most appropriate (Appendix 2). Based on recent literature reporting on antibiotic therapy for DFO [8,16-20], clinicians were free to choose the administration route. For the microbiological diagnosis of DFO, we required several intraoperative tissue/bone samples for culture, but did not require histological examination.

Definitions

We defined DFO according to the criteria of the Infectious Diseases Society of America DFI guidelines [3], which include suggestive radiological, clinical and/or bone microbiological findings. We defined clinical remission of DFO as the complete absence of clinical and radiologic findings of infection after a minimal follow-up of two months after EOT. We defined clinical failure as either recurrent, persistent or new infection at the original site [21], or secondary amputation for progressive infection, ischemia or necrosis. We defined microbiological failure as a microbiologically-confirmed recurrence or persistence at the same localisation with the same pathogen (or at least one of the same pathogens in case of polymicrobial infection). We accepted off-loading as correct if it avoided of all mechanical stress on the infected site during most of the daytime. To assess the wound size (if there was any infected ulcer), we used a custom-made composite score from a prior RCT by our group [13]. This scale (4-30 points) measures wound depth, and visually assesses for undermining of the edges and redness; the score is the sum of the individual points (Appendix 3). An adverse event (AE) was any medical occurrence in a study participant during the trial.

Study Conduct

The full details are available in the Protocol (Appendix 1). The treatment period included the following (inpatient or outpatient) visits: visit 1 – Enrollment (Day 1); visit 2 – Day 8 (± 4 days); visit 3 – Day 20 (± 4 days); visit 4 – Day 40 (± 4 days) (only if still receiving treatment after Visit 3). The Test-of-Cure (TOC) visit occurred at approximately 60 days (± 10 days) after EOT.

Statistical analyses

The primary outcome was clinical remission after a minimum follow-up of two months after EOT. The secondary outcome was the incidence of AEs in each study arm. For both outcomes, our pre-study estimate was an incidence of 80%, based on prior publications [2,3] and data from our medical centre's Clinical Pathway for DFO [9]. Using a binomial categorical, non-inferiority design, with an alpha level of 5%, a power of 80%, we needed 2 x 64 (128) episodes to achieve a non-inferiority margin of 25%. Expecting a dropout of 15%, we aimed to enrol at least 150 episodes for the overall study protocol, including soft tissue infections and DFO together. For DFOs alone, the sample size was at maximum 100 episodes (Protocol summary; Appendix 1). For the formal non-inferiority proofs, we used the *t-test* with a (unidirectional) confidence interval of 90%. To adjust for the expected substantial case-mix, we planned a multivariate cluster-controlled Cox regression analysis with the outcome "clinical remission" (clustering on the individual patients' level). The intention-to-treat (ITT) population consisted of all randomized episodes. The per-protocol (PP) population included all participants who completed the study and whose treatment did not substantially deviate from the study protocol. We used STATA™ software (15.0; College Station, USA).

Results

Study population

Our Clinical Pathway identified 346 DFIs and excluded 187 (54%) for the reasons shown in Figure 1. Excluding the 66 DFI patients who had solely diabetic foot soft tissue infection left 93 DFO episodes for the core analysis (ITT population; Table 1). There were 17 episodes in women (18%); the overall

median subject age was 65 years; the median American Society of Anesthesiologists-Score was 3 points; the median transcutaneous oxygen tension was 38 mmHg (dorsal foot); the median ankle-brachial index was 1; the median serum C-reactive protein level was 76 mg/L; and, the median body mass index was 27 kg/m^2.

Overall, there were 63 different microbiological constellations, including *Staphylococcus aureus* (the most common pathogen, identified in 44 [47%]), streptococci (10, 11%), gram-negative pathogens (28; 30%) and polymicrobial infections (48; 52%). These results were based on a median of 2 bone samples (interquartile range (IQR), 1-3 samples) per patient, although in 40 DFO cases the patient had received empirical systemic antibiotic therapy before bone sampling (prior median antibiotic duration 0 day, IQR, 0-3 d). The infection sites were the toes (n=53), the midfoot (31), and the hindfoot (11) and both the toes and the metatarsal regions (n=2). The comparison of demographic data for the two study arms showed they were well balanced (Table 2).

Treatment

Among the 93 included DFO episodes, 44 randomized to the 3-week arm and 49 to the 6-week arm. Eight (9%) additionally underwent angioplasty and eleven (12%) had hyperbaric oxygen therapy for wound dehiscence. The median number of surgical debridement per episode was 1 (IQR, 0-2 interventions), among which 34 (36%) were partial amputations. We used 47 different antibiotic regimens, which the most frequent agents being co-amoxiclav (63%), levofloxacin (22%), clindamycin (17%), co-trimoxazole (9%), and doxycycline (9%); rifampicin was

administered in only 1 case. The median duration of the initial parenteral therapy was 2 days (IQR, 0-3 d).

Outcomes

Among the DFO episodes, 73 (78%) remained in total clinical remission after an active median follow-up of 11 months (IQR, 5-19 mts). The median passive follow-up (only telephone information or notes in medical files) was 17 months. Among the 20 clinical failures, eight were microbiological recurrences (8/93; 9%): three in the 3-week and five in the 6-week treatment group. These recurrences mostly occurred 15 to 30 days after EOT. The other 12 failures yielded a new pathogen [21]. There was no difference in the incidence of clinical remission between the two study arms (Tables 1 and 2). Remission occurred in 37 of 44 (84%) episodes in the 3-week arm compared to 36 of 49 (73%) in the 6-week arm (p=0.21). The median Wound Score overall decreased from 17 to 4 points, corresponding to a median decrease of 70%. Of note, at the time of database closure at the end of the passive follow-up, new clinical failures occurred in twenty episodes (1 acute Charcot foot and 19 new DFIs), and 26 patients died (after the active study period) for reasons unrelated to the previous DFO episode.

Adverse events

We noted 24 AE in 33 separate episodes (33/93; 35%), of which 14 were serious (SAE). The number of AE was similar in the two study arms (Table 2). While the most serious AE were unrelated to infection (7 acute ischemia, 3 postoperative atelectasis; 2 acute gout), we attributed 11 to the study antibiotic therapy (4

fungal intertrigo; 1 anaphylaxis to co-amoxiclav; 1 drug fever with cotrimoxazole; 3 skin rash to amoxicillin or levofloxacin; 1 severe diarrhea due to levofloxacin; and, 1 persistent nausea with clindamycin). No patient left the study because of an AE. One patient developed a symptomatic urinary tract infection that we treated with another antibiotic agent inactive against the pathogen of DFO.

Per-Protocol analysis

Among the 93 DFO episodes composing the ITT population, we removed eleven (12%) when constituting the PP population (Figure 1). In the PP population, we treated 39 DFO episodes with a 3-week course of antibiotics and 43 during with a 6-week course. In both study arms, the median number of surgical debridement was one. The incidence of clinical remission was similar to the ITT populations: 33 of 39 episodes in the 3-week arm versus 32 of 43 episodes in the 6-week arm (85% vs 74%; p=0.26). The proportion of AE was also similarly distributed: 15/39 in the 3-week versus 13/43 in the 6-week antibiotic arm (p=0.64). AE related to the study antibiotic therapy occurred in 4 in the 3-week versus 5 in the 6-week arm (10% versus 12%, p=0.45).

Multivariate adjustment

Since the antibiotic therapy is only one part of the multipronged treatment program for DFO, we added a cluster-controlled Cox regression analysis further adjusting for non-randomized variables (Table 3). The treatment with the 3-week compared to the 6-week antibiotic course did not correlate with the incidence of

remission (ITT population: HR 1.1, 95%CI 0.6-1.7). The corresponding multivariate result in the PP population was HR 0.8, 95%CI 0.5-1.4.

Non-inferiority

The statistical analysis of the results demonstrates non-inferiority of the shorter to the longer treatment duration. For remission, the confidence intervals excluded the 25%-margin (8.5 difference points [90%CI -24% to +4%] (ITT population). Similarly, there was a statistical non-inferiority for AE (10.0 difference points [90%CI -23% to +10%] (ITT population). The corresponding results in the PP population were 9.0 difference points [90%CI -25% to +5%] (remission) and 6.9 difference points [90%CI -13% to +15%] (adverse events), respectively.

Discussion

The results of our single-center, real-life, pilot study in adult patients with DFO found that a relatively short course (3 weeks) of post-debridement antibiotic therapy was non-inferior to the standard duration of 6 weeks, albeit with a wide statistical margin of 25%. The incidence of clinical remission was 78%, which is similar to other studies in the literature [1-5].

Standard practice in orthopedic surgery has been to treat most types of implant-free osteoarticular infections, after undergoing adequate surgical debridement, with 4-6 weeks of antibiotic therapy [22-24]. Specifically, for DFO, a small French RCT compared a with antibiotic therapy (without surgery) for 6-weeks versus for 12-weeks and found a similar incidence of clinical remission. Based on this landmark study, most clinicians treat DFO for 6 weeks. But, the obvious

question of whether an even shorter duration of antibiotic therapy would be sufficient does not appear to have been evaluated [4]. In this RCT, AE occurred in up to 30% of the episodes, but there was no difference between the two antibiotic treatment duration arms. This finding is in line with previous publications, including our own [15,24-26].

Our RCT has many strengths, but also has five important limitations. *First*, being a pilot study, further stratifications into more distinct populations, such as by the presence of limb ischemia, would require much larger sample sizes. Such RCTs would be difficult to perform, and unlikely to be funded without a prior pilot study.

Second, while our estimated remission incidence of 80% matched well with the observed rate of 78%, our non-inferiority margin of 25% may appear to be too high. We justify this large margin by the non-lethal nature of most DFOs, the fact that this was a pilot study, and that antibiotic agents are only one part (arguably secondary to surgical resection) in the multifaceted treatment of DFO.

Third, our minimal study follow-up period after treatment of two months might seem too short compared to the usual one to two years for implant-related infections. Recurrence of implant-free osteomyelitis can occur during many years after stopping of antibiotics [27]. However, we believe our relatively short follow-up is acceptable for several reasons: i) a short follow-up actually favors the long-treatment arm; ii) with a longer follow-up distinguishing between a recurrence and a new infection is more difficult [21,25]; iii) we found that

recurrences occurred between 15 and 30 days after EOT; and iv), it was designed as a "pilot-study," informing the decision to conduct more comprehensive RCTs in the field.

Fourth, our real-life RCT included DFO episodes in which the subject underwent a partial amputation, which mechanically removes a substantial part of infection, leaving less infected bone for the antibiotics to treat. The proportion of partial amputations was a third (36%) in each arm. In our analyses, we could not detect a protective effect of the variable “partial amputation”. Recent studies suggest that (at least for forefoot DFO) the incidence of clinical remission is similar for patients treated predominantly by antibiotic therapy compared to surgery [1,5,8]. In our study, when excluding all partial amputations (24/27 vs. 20/27; p=0.16), or when excluding all surgical debridement (9/12 vs. 13/15; p=0.44), the 3-week course showed the same outcome as the 6-week course.

We determined if there was persisting bone infection (in case of partial amputation) by pre-surgical radiological and/or intraoperative assessments. This situation differs from that in recent publications, demonstrating that DFO cases with microbiologically-positive margins of bone culture more often fail than cases without proof of missed residual infection [28]. Our setting is the exact opposite, as we left infected bone *in situ* on purpose. There are very few data concerning outcomes in this "inverse problem". Based on our own experience in Geneva, it is far more common to wrongly assume a clear amputation [28] than to remove all infected tissue during surgery that was not intentionally planned to do so beforehand [29].

Fifth, with 63 different microbiological constellations used among the 93 episodes, we cannot compute the role of each individual pathogen on the likelihood of remission. As a general rule for orthopedic infections, including DFOs, the duration of the systemic antibiotic therapy does not depend on the species of isolated bacteria (except for mycobacteria or special pathogens such as actinomycetes or *Nocardia*) [1-5,8]. Indeed, the great majority of retrospective studies have failed to reveal a decisive, independent role of the isolated pathogens, even for methicillin-resistant *Staphylococcus aureus* [30]. In this pilot trial, we were only able to assess the role of the most common pathogen: *S. aureus*, and found that it played no decisive role in the analyses.

Conclusion

Our pilot trial suggests that a shorter duration of antibiotic therapy than currently recommended may be sufficient for treating DFO. These results suggest that there is a need for a larger RCT to see if it confirms our data. We have therefore started the confirmatory RCT with 400 planned episodes in Zurich [9], by using a non-inferiority margin of 10%, a streamlined surgical approach with routine intraoperative biopsies of the residual bone stump, an initial radiological examination by magnetic resonance imaging [14], an evaluation of the nutritional scores and of the glycated hemoglobin levels, and a stratification between surgical versus totally antibiotic treatment approaches. We have also added a new side study investigating the duration of antibiotic therapy needed after total (not partial) amputations [29]. If we confirm our pilot findings, the clinical implications, especially for improved antibiotic stewardship of in the field of DFO [2], might be substantial.

NOTES

Contributors

KG: Study Conduct, Inclusion, Supervision, Writing

TTP: Study Conduct, Inclusion, Supervision

BK: Study Nurse, Conduct, Supervision

FRJ: Drafting, Organization, Inclusion, Supervision

GC: Drafting, Organization

DS: Main Surgeon, Study Conduct, Supervision

JP: Original Idea, Drafting, Organization

BAL: Idea, Concept, Writing, Corrections

IU: Idea, Concept, Drafting, Sponsor, Principal Investigator, Inclusion, Conduct, Supervision, Analyses, Writing

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Potential conflict of interests

None of the authors have any financial or other conflict of interest in connection with this work.

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Figure legends

Figure 1: Study Flowchart

Table 1. Characteristics and outcomes of subjects with a diabetic foot osteomyelitis episode by duration of treatment with systemic antibiotic therapy after debridement (intention-to-treat population)

	Duration of antibiotic therapy		
	Three weeks	**Six weeks**	*p*-
n = 93	n = 44	n = 49	value *
Clinical			
Female sex	6 (14%)	11 (22%)	.27
Median age	70 years	65 years	.23
Median body mass index	27 kg/m^2	28 kg/m^2	.89
Osteomyelitis involving toe	22 (50%)	31 (63%)	.20
Charcot midfoot deformities	6 (14%)	6 (12%)	.84

Clinical peripheral arterial disease	27 (61%)	26 (53%)	.42
Transcutaneous O_2 tension (dorsal foot; median)	36 mmHg	41 mmHg	.58
- Successful angioplasty performed	4 (9%)	4 (8%)	.87
Wound Score at admission (median)	16 points	17 points	.56
Pathogens			
Staphylococcus aureus	21 (48%)	23 (47%)	.94
Gram-negative bacteria	11 (25%)	17 (35%)	.31
Polymicrobial infection	20 (45%)	28 (57%)	.26
Therapy			
Number of surgical debridement (median)	1 intervention	1 intervention	.27
- Partial amputations	16 (36%)	18 (36%)	.97

Hyperbaric O_2 therapy	6 (14%)	5 (10%)	.61
Duration of intravenous therapy (median)	1 day	3 days	.37
Outcomes			
Complete remission	37 (84%)	36 (73%)	.21
- Microbiological recurrences only	3 (7%)	5 (10%)	.56
Adverse events	17 (39%)	16 (33%)	.54
- Serious adverse events	5 (11%)	9 (18%)	.35
- Antibiotic-related adverse events	4 (9%)	7 (14%)	.44
Complete wound healing after therapy	28 (64%)	29 (59%)	.67

*Pearson χ^2-test or Wilcoxon-ranksum-tests. Significant results (p <0.05) are indicated ***in bold and italic***

Table 2. Characteristics of cases in which there was a clinical remission versus a clinical failure (intention-to-treat population)

Diabetic foot osteomyelitis	**Clinical Failure**	**Clinical Remission**	*p*-
n = 93	n = 20	n = 73	value *
Female sex	2 (10%)	15 (21%)	.28
Median age	62 years	68 years	***.02***
Osteomyelitis involving toe (vs another anatomic site)	12 (60%)	41 (56%)	.76
Lower extremity angioplasty performed	0 (0%)	8 (11%)	.12
Osteomyelitis due to *Staphylococcus aureus*	12 (60%)	32 (44%)	.10
Number of surgical debridements (median)	1 intervention	1 intervention	.83
- Partial amputations	9 (45%)	25 (34%)	.38

Three-week course of antibiotic therapy	7 (35%)	37 (51%)	.21
Estimated % with adequate adherence by nurses/clinicians	18 (90%)	59 (81%)	.34
Length of hospital stay (median)	13 days	10 days	***.87***

* Pearson χ^2-test or Wilcoxon-ranksum-tests. Significant results (p <0.05) are indicated ***in bold and italic***

Table 3. Univariate and multivariate associations with the outcome "clinical remission" in the intention to treat (ITT) and per protocol (PP) populations

(Cox regression analysis; results expressed as hazard ratios with 95% confidence intervals)

ITT Population	**Univariate**	**Multivariate**	**PP Population**	**Univariate**	**Multivariate**
n = 93			n = 82		
Demographics					
Female sex	0.9, 0.5-1.6	-	Female sex	1.0, 0.5-1.9	-
Age	1.0, 1.0-1.0	-	Age	1.0, 1.0-1.0	-
Body mass index	1.0, 0.9-1.0	-	Body Mass Index	1.0, 0.9-1.0	-
Toe osteomyelitis	1.0, 0.6-1.7	-	Toe osteomyelitis	1.2, 0.7-2.1	-
Peripheral arterial disease	0.9, 0.5-1.5	-	Peripheral arterial disease	0.9, 0.5-1.6	-
Ankle-brachial index	0.7, 0.2-1.9	-	Ankle-Brachial Index	0.8, 0.3-2.2	-
- Angioplasty	1.4, 0.6-3.2	1.6, 0.8-3.2	- Angioplasty	1.9, 0.8-4.6	1.9, 0.9-3.8
Wound Score (size) at admission	1.0, 1.0-1.0	-	Wound Score (size) at admission	1.0, 0.9-1.0	-
Pathogen			*Pathogens*		
Staphylococcus aureus	1.1, 0.7-1.9	1.4, 0.8-2.4	*Staphylococcus aureus*	1.1, 0.6-1.8	1.3, 0.8-2.1
Gram-negative bacilli	0.9, 0.5-1.5	-	Gram-negative bacilli	1.0, 0.5-1.7	-

Polymicrobial infection	1.4, 0.8-2.3	-	Polymicrobial infection	1.3, 0.7-2.2	-
Therapy			*Therapy*		
3-week antibiotic therapy arm	1.0, 0.6-1.6	1.1, 0.6-1.7	Short (3-week) antibiotic therapy	0.8, 0.4-1.3	0.8, 0.5-1.4
Intravenous antibiotic duration	1.0, 1.0-1.0	1.0, 1.0-1.0	Intravenous antibiotic duration	1.0, 1.0-1.0	1.0, 1.0-1.0
Number of surgical debridement	1.0, 0.8-1.2	-	Number of surgical debridement	1.1, 0.8-1.5	-
- Partial amputations	0.7, 0.4-1.2	***0.5, 0.2-0.9***	- Partial amputations	0.6, 0.3-1.1	0.5, 0.3-1.0
Adequate patient adherence	0.9, 0.5-1.7	-	Adequate patient's adherence	0.6, 0.3-1.2	-

* Statistically significant results are displayed ***in bold and italic***. " - " = not included in the multivariate model

Figure 1